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10/518,503	12/20/2004	Hans-Michael Eggenweiler	MERCK-2957	7857

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EXAMINER	
JAISLE, CECILIA M	
ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,503	EGGENWEILER ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Dec. 20, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

The holding of Lack of Unity is withdrawn. All claims are under examination.

Rejection Under 35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 29 is rejected under 35 USC 112, second paragraph, as indefinite and incomplete in not defining a completed article of manufacture. The Court of Customs and Patent Appeals, in *In re Venezia*, 189 USPQ 149 (C.C.P.A. 1976), described criteria for a proper kit or package claim under 35 USC 112, second paragraph, which the present kit claims do not satisfy. The claims do not include present structural limitations on each kit element, nor do they include structural limitations defined by how the elements interconnect in the final kit assembly. No structural configuration for the kit is defined in accordance with how the kit elements interrelate with each other in the completed kit assembly. The claims do not positively recite any structural relationship among the kit or package elements.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim subject matter that applicant regards as the invention.

In claim 1, the definition of V and W should be corrected to recite that they may be "oxygen or **two** hydrogen substituents." The definition in claim 1 of A" and A"' as "absent" should be corrected to recite --a bond--.

In claim 16, the compounds are mis-named as 5,6-dihydro-4H-pyridazines, without specifying the hydrogenation of the 3-position, when the compounds are correctly 3,4,5,6-tetrahydropyridazines. Correction is required.

In claims 1-29, the term "derivative" has no specific set meaning. The term "derivative" may mean a residue or a different compound derived from the recited formula I compound, and is therefore not possible to know which derivatives are envisaged as derived from the formula I compound. The attached reference to Wikipedia shows that the term "derivative" refers to:

> ...a compound that is formed from a similar compound or a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms.

"Derivatives" is of unknown scope. What does it cover? Does it include halogenated versions? Dimerized or polymerized versions? Versions with the right (left) side substituent of the molecule lopped off? With a multiple bond hydrogenated? With the N or S oxidized to the amine oxide or sulfoxide? Can rings be opened? Chains extended or contracted in length? Can substituents couple together to form a ring? Can atoms be replaced with others atoms, and if so, what sorts of replacements can be made? For example, could NH, O, or S replace a CH_2 group, or vice versa? Could P or CH replace N, or vice versa? There is no generally accepted definition of what constitutes a derivative, and hence, one does not know where the line is between

things that are derivatives and things that are transformed too much to be derivatives. How can one of ordinary skill in the art tell what is intended? Deletion is suggested.

In claims 19, 22, phrases including such phrases as "if desired," and "for example," render the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

In claims 20-26, the reference to "phosphodiesterase-4" is unclear. Four genes encode the PDE-4 family; there are actually four PDE-4 types, PDE-4A, PDE-4B, PDE-4C and PDE-4D, and these also occur in isoforms. These generally arise from presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2) and other pieces that may be present. UCR1 and UCR2 are shown to form a module necessary for PDE-4 activation upon cAMP-dependent kinase (PKA) phosphorylation. E.g., at least 5 different forms of PDE-4B: PDE-4B1, PDE-4B2 (the short form), PDE-4B3, PDE-4B4 exist and very recently discovered, PDE-4B5. Distinct PDE-4A isoforms include PDE-4A1, PDE-4A5, PDE-4A4B, PDE-4A7, PDE-4A8, PDE-4A10 and PDE-4A11. PDE-4D has 9 forms, which are not necessarily interchangeable and have substantial distribution variation even within sub-families. Thus, PDE-4A1 is abundant in the brain, PDE-4A4B and PDE-4A10 in inflammatory cells, PDE-4A7 in the brain and spleen, and PDE-4A11 is widely distributed. The PDE-4D family is generally not seen in inflammatory cells. PDE-4D1 is seen in spleen and heart, PDE-4D2 in spleen, PDE-4D3 in brains, lung and kidney, PDE-4D4 and PDE-4D6 in brain, PDE-4D5 in lung and kidney, PDE-4D7 in brain and testes, PDE-4D8 in lung, heart and liver, and PDE-4D9 in spleen, heart and lung.

Different types are differently regulated. ERK MAP kinases phosphorylate and regulate activity of PDE-4B, PDE-4C and PDE-4D but not PDE-4A isoforms. Reduced PDE-4D activity apparently causes defective RyR2-channel function associated with heart failure and arrhythmias. In dendritic cells (cells responsible for naive T_h cell priming), PDE-4A is predominantly active, whereas monocytes mainly express PDE-4B. PDE-4D5 isoform preferentially interacts with signaling scaffold proteins, β-arrestin and RACK1. PDE-4D3 likewise forms a signaling complex with AKAPs, e.g., AKAP450. See the Wikipedia discussion of phosphodiesterase.

In Claim 22, the definition of septic shock as "selected from the group consisting of ..." is indefinite and confusing. The various conditions recited as forms of septic shock may possibly cause septic shock, but none of them is itself a type of septic shock.

In claim 27, the use of codes to identify therapeutic agents is indefinite, because the manufacturer can change the meaning of the codes at will.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for making pharmaceutically usable derivatives of the formula I compounds embraced thereby. The specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims,

insofar as they embrace "derivatives." There is no way to know what these derivatives encompass. There is no way to tell how to make them or what properties they will have.

Claims 20 – 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably enable treatment of all pathological conditions/diseases susceptible to phosphodiesterase-4 (PDE-4) inhibition amelioration with Formula (I) compounds. The present specification offers no evidence that the claimed compounds control specific diseases/conditions susceptible to PDE-4 inhibition amelioration, although the claims encompass such diseases/conditions. The specification otherwise does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims. The following reasons apply to this enablement rejection.

Pursuant to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue;" see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds.

The scope of the compounds is the trillions of compounds comprehended under formula I, even without the inclusion of the unknown and unknowable "derivatives." Further, the claims cover unknown "derivatives," whose properties may be entirely different. The term "derivative" may be interpreted as a residue or a different compound derived from the recited formula I compound, and is therefore confusing as to which derivatives are envisaged as derived from the formula I compound. The attached Wikipedia reference shows that the term "derivative" refers to:

> ...a compound that is formed from a similar compound or a compound that can be imagined to arise from another compound, if one atom is replaced with another atom or group of atoms.

The specification does not teach how to make all possible derivatives of the compounds of formula I. Because the specification does not teach how to prepare all such derivatives, undue experimentation will be required to practice Applicants' invention. Based on the nebulous meaning of the term "derivatives," those of skill in this art would be at a loss as to how to make and use all derivatives of the compounds of formula I. The specification describes the intention to prepare derivatives of the compounds of formula I, without teaching the preparation and necessary starting materials to prepare such derivatives.

(b) Scope of the diseases covered.

Under diseases caused by PDE 4 isozyme is Chronic Obstructive Pulmonary Disease (COPD), a collection of slowly progressive diseases of the airways, characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself. Chronic Obstructive Pulmonary Disease (COPD) is a collection of slowly progressive airway diseases, characterized by gradual lung function loss. COPD includes chronic obstructive bronchitis (inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including congenital lobar emphysema, bullous

emphysema, centrilobular emphysema (proximal acinar emphysema), panacinar (panlobular), distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, a genetic form of emphysema. COPD patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. COPD has no pharmaceutical treatment per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for lung function loss. Bronchodilators can expand lung passageways, corticosteroids can reduce inflammation and antibiotics can ward off bacterial infections, but none of these treat COPD itself. See the discussion of COPD in Wikipedia.

IBD is a generic term for an entire disorder family, the most important of which are Ulcerative colitis and Crohn's disease. Less common forms include lymphocytic colitis, collagenous colitis, radiation enterocolitis, solitary rectal ulcer syndrome (SRUS), Antibiotic associated IBD, diversion colitis, Ischaemic Colitis, Behçet's Syndrome, and Infective Colitis. IBD arises from a range of causes, known and unknown. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Ischaemic Colitis arises from partial death tissue (infarct) due to blood supply blockage, e.g., after major abdominal surgery or poor cardiac output in heart disease. Radiation enterocolitis arises from cancer chemotherapy. Infective Colitis can arise from bacteria (e.g., Shigella, Salmonella, Campylobacter, E. coli) or Viruses (e.g., Norwalk-like virus

rotavirus, CMV and HSV). Diversion Colitis develops from faecal stream diversion following colostomy or ileostomy. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no effective pharmaceutical treatment. IBD is a generic term for a family of disorders, of which ulcerative colitis and Crohn's disease are most important. Less common forms are colitis (including lymphocytic, collagenous, diversion, ischemic and infective colitis), radiation enterocolitis, solitary rectal ulcer syndrome (SRUS), antibiotic associated IBD, and Behçet's Syndrome. IBD has a range of known and unknown causes. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Partial tissue death (infarct) due to blood supply blockage, e.g., after major abdominal surgery or poor cardiac output in heart disease, can cause ischemic colitis. Cancer therapy can cause radiation enterocolitis. Infective colitis can arise from bacteria (e.g., shigella, salmonella, campylobacter, E. coli) or viruses (e.g., Norwalk-like virus rotavirus, CMV, HSV). Fecal stream diversion after ileostomy or colostomy can cause diversion colitis. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no current effective pharmaceutical treatment. See the Wikipedia discussion of IBD.

Memory disorders comprise all impairment of understanding or skill disorders. These include acquired language disorders, such as aphasias (e.g., conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia. It includes many types disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory

about one specific event), Fugue amnesia (Psychogenic amnesia or hysterical amnesia, including "repressed memories"), Childhood amnesia (inability to remember events from early childhood), Transient Global Amnesia (total memory loss), those arising from complex partial seizures, and alcoholic blackouts. It also includes various agnosias, such as Prosopagnosia, Integrative agnosias, asogmatoagnosia, Associative agnosias, Time Agnosia, Apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia, dyslexia, dyscalculia, right-left disorientation, Optic ataxia and Ocular apraxia, Color Agnosia, Simultanagnosia, Anosognosia, Auditory Agnosia (including amusia and word meaning deafness), and Somatosensory Agnosia (including Microsomatagnosia, Macrosomatagnosia, tactile agnosias and astereoagnosia), constructional dyspraxia, and more general processing disorders such as Cerebral Visual Impairment (CVI).

The attached printout from MedLinePlus <http://www.nlm.nih.gov/medlineplus/infections.html>, downloaded June 29, 2007, provides a partial list of disorders/conditions embraced under the term "infections," for the vast majority of which the present specification provides no enabling treatment.

The attached printout from MedLinePlus <http://www.nlm.nih.gov/medlineplus/cancers.html>, downloaded June 29, 2007, provides a partial listing of diseases/conditions embraced under the term "cancers," for the vast majority of which the present specification provides no enabling treatment.

The claims also embrace dozens of immune disorders.

The claimed scope includes treating various disorders/diseases, which are inadequately enabled, based on inhibition of PDE-4. The compounds of Formula (I) are disclosed to inhibit PDE-4 and the specification recites that these compounds are therefore useful to treat all diseases susceptible to amelioration by PDE-4 inhibition for which Applicants provide no competent evidence. Further, Applicants have not provided competent evidence that the instantly disclosed tests (pages 21-28, *inter alia*) are highly predictive for all uses disclosed and embraced by the claim language for the intended host.

Claims 20-26 are directed to methods for treating conditions or diseases susceptible to PDE-4 inhibition amelioration. The claimed scope includes the recited disorders of the claims, as well as other known and as-yet undiscovered disorders/conditions that may be associated with PDE-4 now or in the future, for which the disclosure is non-enabling.

(2) The nature of the invention and predictability in the art:

The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance:

That provided is very limited. The dosage range information (page 83+, *inter alia*) is vague and meager. Even the broadest range is 25 fold. Moreover, this is generic,

the same for the many disorders covered by the specification. There is no specific direction or guidance regarding a regimen or dosage effective specifically for various compounds described for various medical conditions comprehended. The prior art does not provide an available source for all starting materials necessary to prepare all derivatives of the compounds formula I. While the claims recite **derivatives,** no working examples show their formation.

(4) State of the Prior Art:

These compounds are tetrahydropyridazine and dihydropyridazone derivatives with a particular 2-position substitution pattern. So far as the examiner is aware, no such tetrahydropyridazines and dihydropyridazones of any kind have been determined to have PDE-4 inhibition activity, nor to useful for the treatment of the various diseases construed by the claims. No derivatives of any kind of the compounds of formula I have been determined to have PDE-4 inhibition activity, or to be used for treatment of various diseases the claims construe.

The comments of Dyke, et al., Exp. Opin. Invest. Drugs 8:1301-1325 (1999), on PDE-4 inhibitor efficacy in Parkinson's disease and learning and memory impairment are prophetic. Regarding MS, Dyke suggests, with no clinical data available, that PDE4 inhibitors may be useful as anti-inflammatory agents, but not as disease modifying agents (pg. 1313). Dyke's expert opinion was that, although PDE-4 inhibitors showed promise in the respiratory area, "clinical data in most [other] therapeutic areas with compounds of this class is inconclusive" (pg. 1314). Dyke acknowledges various PDE

isoenzymes, but teaches that PDE-4 inhibitors have only been implicated for anti-inflammatory conditions (pg. 1302).

Hanifin, et al., Journal of Investigative Dermatology, 107(1):51-56 (1996) reported testing CP80633, CP102995 and CP76593, PDE-4 inhibitors, on atopic dermatitis. Although Hanifin demonstrated clinical efficacy, later researchers, Griffiths, et al., British J. of Dermatology 2002: 147, 299-307, noted that CP80633 was "the only PDE-4 inhibitor known to be clinically effective in atopic dermatitis" (page 300). Thus, Hanifin and Griffiths support that not all PDE-4 inhibitors, such as the claimed compounds, are effective against atopic dermatitis.

PDE-4 predominates in inflammatory cells and, specifically, modulates leucocyte activation. PDE-4 inhibitors would be expected to produce bronchodilation and have a certain anti-inflammatory effect, in particular, blocking mediator synthesis (and release) in mast cells and basophiles.

The concept that PDE-4 inhibitors could treat such pathological conditions/diseases generally is contrary to what is known about PDE-4 inhibitors. Some PDE4 inhibitors cause vasculitis (blood vessel inflammation), which has hindered PDE-4 inhibitor clinical investigation. Development of SCH-351591 halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was a significant problem with CI-1018 and Ariflo® (cilomilast). The PDE-4 inhibitor IC542 triggered a generalized inflammatory response with extensive neutrophil infiltration in the gastrointestinal tract, nearby mesentery and thymus.

(5) Working Examples:

Examples 1-7 show the production of a meager number of compounds from among the trillions covered by formula I. No biological data of any kind is presented. The working examples do not show formation of any derivatives of compounds of formula I. As stated in *Morton Intrntl. Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (Fed.Cir. 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The specification shows no evidence of the preparation and starting materials for all derivatives of the compounds of formula I. Hence, Applicants must show formation of such derivatives or limit the claims accordingly.

(6) Skill of those in the art:

The history of the actual effectiveness of PDE-4 inhibitors is very short. PDE-4 inhibitors have been investigated for disorders ranging from AD to COPD to depression to schizophrenia to chronic lymphocytic leukemia (CLL). Except in the area of asthma, such efforts have met with very little success. The skill level in the area of PDE-4 therapeutics must therefore be considered to be low. At the time of filing and up to now, FDA has not approved any PDE-4 inhibitor for any disorder treatment. Extensive effort to get cilomilast and Daxas® (roflumilast) to be effective against COPD has been without success, evidence of the skill level in this art. Whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast is not described.

Many if not most diseases said to be treatable by PDE-4 inhibition, e.g., allergic rhinitis, osteoarthritis, osteoporosis, bone-formation disorders, multiple sclerosis (MS), ankylosing spondylitis, glomerulonephritis, Graves ophtalmopathy, myasthenia gravis, diabetes insipidus, graft rejection, gastrointestinal disorders, ulcerative colitis, Crohn's disease, septic shock, adult distress respiratory syndrome, contact dermatitis, acute dermatomyositis, dementia, Alzheimer's disease (AD), depression, etc., are hard to treat. At present no known drug successfully reverses the course of many of these diseases, including MS, AD, etc., despite many drugs said to inhibit PDE-4.

The state of the art indicates the requirement for undue experimentation. MacKenzie, Alergology International (2004) 53:101-110, indicates that, although the new generation of PDE-4 inhibitors "display[s] greatly reduced side-effects, ... further study of the potential ancillary involvement of adrenaline and/or glucocorticoids in the enhancement of PDE-4, shown in blood mononuclear white cells of [atopic dermatitis] patients is warranted." The ability of a PDE-4 inhibitor to ameliorate all diseases/conditions of the present claims remains open to further study and proof.

Regarding viral infections, the Viral Defense Found., <http://www.viraldefense.org/mission.htm>, downloaded 5-23-07, states, "Most viral infections are essentially untreatable after infection occurs." Similarly, the Visiting Nurse Assns. of America, <http://www.vnaa.org/vnaa/gen/Germ_Protection_Center_Cold_and_Flu_Resources,html...>, downloaded 5-23-07, notes, "Most viral infections are untreatable..."

Compounds that affect the virus itself, which has not been established here, cannot treat viral infections.

(7) The quantity of experimentation needed:

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. See also MPEP 2163, *et. seq.* The disclosure in this application is insufficient to enable the instantly claimed methods based solely on disclosure of PDE-4 inhibition by Formula (I) compounds. Based on the disclosure content, determining if the claimed derivatives could be prepared would require determining if their starting materials are commercially available and if methods of making these claimed derivatives could be devised without the exercise of inventive skill, particularly when the identity and structure of such derivatives is unelucidated by the specification. Such experimentation is potentially open-ended.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stereoisomers of the compounds of Formula I, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, insofar as they embrace solvates, are not enabled. The numerous examples presented all failed to produce a solvate. The evidence of the specification is thus clear: These compounds do not possess the property of forming solvates; there is no evidence that such compounds even exist. Thus, this is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190: "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist." The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

MARK L. BERCH
PRIMARY EXAMINER
GROUP 120 - ART UNIT 1624